CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-323

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 21-323 **CHEM REVIEW: #1** **REVIEW DATE: 08/31/01**

SUBMISSION TYPE	DOC DATE	CDER	ASSIGNED	ACTION
ORIGINAL	03/23/01	03/23/01	03/28/01	Information Request, 08/31/01

NAME AND ADDRESS OF APPLICANT

Forest Laboratories, Inc.
Harbor Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

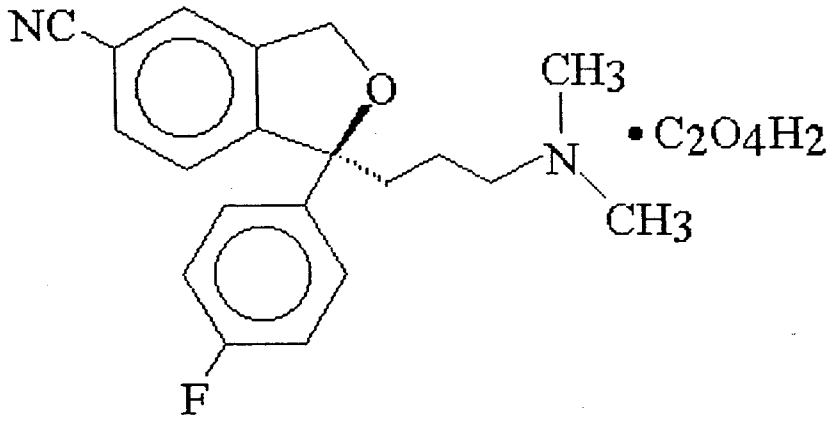
DRUG PRODUCT NAME

Proprietary:	N/A
Non proprietary/USAN:	Escitalopram oxalate
Code Name:	Lu 26-054 (base) Lu 26-054-O (oxalate salt)
Chem. Type/Theraputic Class:	S3

PHARMACOLOGICAL CATEGORY/INDICATION:	
DOSAGE FORM:	Tablet
STRENGTHS:	5 mg, 10 mg, 20 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	X Rx ___OTC
SPECIAL PRODUCTS:	___Yes X No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: S-(+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. oxalate
USAN Name: Escitalopram oxalate
Chemical Formula: $C_{20}H_{21}FN_2O$ (base); $C_{20}H_{21}FN_2O$, $C_2H_2O_4$ (oxalate salt)
Molecular Weight: 324.40 (base); 414.42 (oxalate salt)
CAS Registry Number: 128196-01-0 (Lu 26-054 (base)); 219861-08-2 (Lu 26-054-0 (base))
Laboratory code: Lu 26-054-B (base); Lu 26-054-O (oxalate)
Synonyms: N/A



CHEMISTRY REVIEW

NDA/ANDA 21-323

Escitalopram Oxalate Tablet

Forest Laboratories, Inc.

Lorenzo Rocca
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-323

2. REVIEW # 2

3. REVIEW DATE: 12/6/01

4. REVIEWER: Lorenzo Rocca

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
ORIGINAL	3/23/01
Discipline Review Letter	8/31/01
Amendment	10/16/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	10/16/01

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest Laboratories, Inc.
Address:	Harbor Financial Center Plaza Three, Suite 602 Jersey City, NJ 07311
Representative:	Daniel T. Coleman, Ph.D.
Telephone:	201-386-2126

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Escitalopram Oxalate

c) Code Name/# (ONDC only): Lu 26-054 (base), Lu 26-054-O (oxalate salt)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5, 10, 20 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

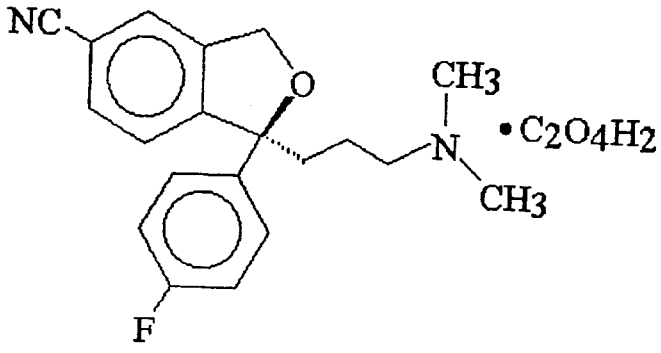
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: S-(+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
Molecular Formula: $C_{20}H_{21}FN_2O$ (base); $C_{20}H_{21}FN_2O$, $C_2H_2O_4$ (oxalate salt)
Molecular Weight: 324.40 (base); 414.42 (oxalate salt)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	H.Lundbeck	API	1	Adequate	7/10/01	N/A
	III			4	N/A	N/A	N/A
	III			1	Adequate	8/21/01	N/A
	III			1	Adequate	8/11/99	N/A
	III			4	N/A	N/A	N/A
	III			1	Adequate	8/6/98	N/A
	III			1	Adequate	8/21/01	N/A
	IV			1	Adequate	8/31/01	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
IND Amendment		Lu 26-054-O
IND Amendment		Primary Stability Matrix
		Specification Revision

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	N/A	N/A	N/A
Pharm/Tox	Approvable	10/17/01	Paul L. Rooney, Ph.D.
Biopharm	Approvable	11/20/01	Iftekhar Mahmood, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Lorenzo Rocca, Ph. D.
OPDRA	N/A	N/A	N/A
EA	N/A	N/A	N/A
Microbiology	N/A	N/A	N/A

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	N/A	N/A
EES	N/A	N/A	N/A
Methods Validation	N/A	N/A	N/A
Labeling	N/A	N/A	N/A
Bioequivalence	N/A	N/A	N/A
EA	N/A	N/A	N/A
Radiopharmaceutical	N/A	N/A	N/A

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Executive Summary Section

The Chemistry Review for NDA 21-323

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-323 is deficient because the proposed site for the manufacture of the API, Escitalopram Oxalate, received a Withhold recommendation (dated 10/11/01) from the Office of Compliance following cGMP inspection of the facility on 8/13/01. NDA 21-323 is therefore recommended "not approvable" for CMC.

The applicant has adequately responded (see NDA 21-323 Amendment dated 10/16/01) to the CMC deficiencies listed in the FDA Discipline Review Letter dated 8/31/01.

Methods validation will be submitted after all CMC deficiencies have been addressed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Escitalopram Oxalate Tablets (5, 10, 20 mg/tablet) are white to off-white, round, biconvex coated tablets. The 10 mg and 20 mg tablets are scored. The 5 mg tablet is not scored. The commercial drug products are similar in shape and color but different in size and weight. All three strengths are debossed on the upper face with the letters "FL" and on the lower face with the numerical strength (i.e., "5", "10" and "20"). The three strengths are packaged in 30, 100 and 1000 count white/opaque HDPE square bottles which uses ——— with either a plastic-over-metal CRC (30 and 100 count) or metal screw cap (1000 count). In addition, each strength is packaged in ———).

The citalopram chemical entity and the chemical synthesis of citalopram have been developed and patented by H. Lundbeck (Copenhagen, Denmark). Lundbeck first introduced citalopram as an antidepressant in Denmark in 1989. Forest Laboratories markets the racemic form of citalopram HBr formulated as a coated tablet (NDA 20-822, submitted May 7, 1997, approved July 17, 1998), and oral solution (NDA 21-046, submitted November 2, 1998, approved December 22, 1999). The citalopram molecules contains one asymmetric carbon with the clinical activity residing in the S-(+) stereoisomer. S-citalopram oxalate (Lu 26-054-O) was discovered and patented

by Lundbeck who has licensed the drug to Forest Laboratories. The method of synthesis of S-citalopram oxalate is based on the synthesis of racemic citalopram HBr. The manufacture of racemic citalopram HBr is described in Lundbeck's Type II ——— The desired S-enantiomer is obtained using commercial scale chiral separation of a late stage intermediate. The manufacture of S-citalopram oxalate is described in Lundbeck's Type II ———. The Escitalopram Oxalate drug substance is released for manufacturing Escitalopram Oxalate Tablets based on the COA from Lundbeck and confirmation of identity by Forest, in addition, Forest will perform at minimum full release tests using the Lundbeck procedures on at least on lot of Escitalopram Oxalate drug substance per year.

Escitalopram Oxalate tablets are manufactured by a ——— The inactive excipients are USP/NF grade, and the non-compendial excipient ———) film coat is adequately described in ——— The normal in-process and physical parameters (e.g., compression parameters, tablet testing frequency, appearance, running tablet weight, hardness, thickness, etc) are monitored during the manufacturing process to assure the quality of the final product.

Clinical supply tablets were of fixed weight (for blinding) while the commercial tablets are dose proportional with a common master blend used to manufacture the different strengths. Minor formulation changes have occurred during drug product development. The major formulation change made during development was the introduction of film coating for the tablets. Manufacturing changes in the final phase of development include introduction of a dose proportional Escitalopram oxalate formulation for the manufacture of the different strengths, introduction of manufacturing changes necessary to scale-up batch size ——— depending on strength) and introduction of the Intermediate Bulk Container (IBC) system for mixing and compression. The IBC system for commercial manufacture of Escitalopram Oxalate Tablets was discussed and agreed upon at the pre-NDA meeting. Three tablet lots (one of each strength) using the IBC system are currently on stability. The differences between the clinical and commercial formulations are not deemed great enough from a chemistry standpoint to cause concern that compatibility studies are needed.

B. Description of How the Drug Product is Intended to be Used

The recommended dose of Escitalopram Oxalate Tablet is 10 mg once daily for all patients. Patients not responding to a 10 mg dose may benefit from a dose increase to 20 mg after a minimum of one week.

Based on the 18-month controlled room temperature (25±2°C/60±5%RH) and 6-month accelerated (40±2°C/75±5%RH) stability results submitted for Escitalopram Oxalate Tablets, packaged as intended for commercial distribution in 30 count, 100 count and 1000 count HDPE bottles and ——— , a 24–month expiration

period (shelf-life), is acceptable when stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-323 is Not Approvable for CMC. The "Not Approvable" recommendation is based on the following major chemistry issue:

- 21CFR210.1(b) Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General states:

  The failure to comply with any regulations set forth in this part and in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as person who is responsible for the failure to comply, shall be subject to regulatory action.

  The proposed site for the manufacture of Escitalopram Oxalate ([redacted] (CFN 9611872)) received, on October 11, 2001, a Withhold recommendation from the Office of Compliance following cGMP inspection of the facility on August 13, 2001. A warning letter, dated October 11, 2001, has been issued.

Before NDA 21-323 can be approved for CMC the proposed site for manufacture of Escitalopram Oxalate needs to be inspected for cGMP and receive an acceptable recommendation from the Office of Compliance. Alternatively, the applicant can withdraw the [redacted] facility from their NDA, and propose an alternative facility for the manufacture of Escitalopram Oxalate. The new facility will need its own acceptable recommendation from the Office of Compliance with regard to manufacture of Escitalopram Oxalate before NDA 21-323 can be recommended for approval for CMC.

The applicant in their NDA Amendment, dated October 16, 2001, has adequately responded to the NDA 21-323 CMC deficiencies previously noted in Chemistry Review No. 1 (August 31, 2001), and conveyed to the applicant in the FDA Discipline Review Letter, dated August 31, 2001.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

LRocca/Date
RSeevers (TL)/Date
PDavid (PM)/Date

C. CC Block

Orig. NDA 21-323
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/RSeevers

APPEARS THIS WAY
ON ORIGINAL

Chemistry Assessment

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

17 pages

Number of Pages Redacted 44

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Confidential,
Commercial Information

CHEMISTRY REVIEW

NDA/ANDA 21-323

Escitalopram Oxalate Tablet

Forest Laboratories, Inc.

Lorenzo Rocca
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-323

2. REVIEW # 3

3. REVIEW DATE: 1/22/02

4. REVIEWER: Lorenzo Rocca

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
ORIGINAL	3/23/01
Discipline Review Letter	8/31/01
Amendment	10/16/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	10/16/01

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest Laboratories, Inc.
Address:	Harbor Financial Center Plaza Three, Suite 602 Jersey City, NJ 07311
Representative:	Daniel T. Coleman, Ph.D.
Telephone:	201-386-2126

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: pending (see item 18 below)
b) Non-Proprietary Name (USAN): Escitalopram Oxalate (= USAN)

c) Code Name/# (ONDC only): Lu 26-054 (base), Lu 26-054-O (oxalate salt)
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Depression

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5, 10, 20 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

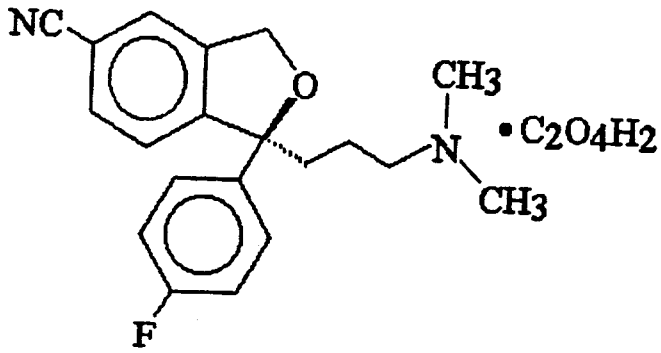
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CA Name: S-(+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
Molecular Formula: $C_{20}H_{21}FN_2O$ (base); $C_{20}H_{21}FN_2O$, $C_2H_2O_4$ (oxalate salt)
Molecular Weight: 324.40 (base); 414.42 (oxalate salt)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	H.Lundbeck	API	1	Adequate	7/10/01	N/A
[redacted]				4	N/A	N/A	N/A
[redacted]				1	Adequate	8/21/01	N/A
[redacted]				1	Adequate	8/11/99	N/A
[redacted]				4	N/A	N/A	N/A
[redacted]				1	Adequate	8/6/98	N/A
[redacted]				1	Adequate	8/21/01	N/A
[redacted]				1	Adequate	8/31/01	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	[redacted]
IND Amendment	[redacted]	Primary Stability Matrix
IND Amendment	[redacted]	Specification Revision

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	1/10/02	Office of Compliance
Pharm/Tox	Approvable	10/17/01	Paul L. Rooney, Ph.D.
Biopharm	Approvable	11/20/01	Iftekhar Mahmood, Ph.D.
LNC	USAN available	N/A	N/A
Methods Validation	Pending	Pending	Lorenzo Rocca, Ph. D.
OPDRA	Trade Name [redacted] Unacceptable; Proprietary Name Lexapro Acceptable	9/4/01	Jerry Phillips
EA	Categorical Exclusion Granted	N/A	N/A
Microbiology	N/A	N/A	N/A

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-323

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-323 is no longer deficient for the following reasons: 1) the applicant has adequately responded (see NDA 21-323 Amendment dated 10/16/01) to the CMC deficiencies listed in the FDA Discipline Review Letter dated 8/31/01, and 2) the Office of Compliance has found acceptable from a cGMP standpoint the supplier of Escitalopram Oxalate API (i.e.,) for NDA 21-323.

NDA 21-323 methods validation package submission, to the appropriate FDA testing laboratory, is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Escitalopram Oxalate Tablets (5, 10, 20 mg/tablet) are white to off-white, round, biconvex coated tablets. The 10 mg and 20 mg tablets are scored. The 5 mg tablet is not scored. The commercial drug product strengths are similar in shape and color but different in size and weight. All three strengths are debossed on the upper face with the letters "FL" and on the lower face with the numerical strength (i.e., "5", "10" and "20"). The three strengths are packaged in 30, 100 and 1000 count white/opaque HDPE square bottles which uses with either a plastic-over-metal CRC (30 and 100 count) or metal screw cap (1000 count). In addition, each strength is packaged in

The drug substance is the S-enantiomer of racemic citalopram. The racemic citalopram chemical entity and the chemical synthesis of racemic citalopram have been developed and patented by H. Lundbeck (Copenhagen, Denmark). Lundbeck first introduced recemic citalopram as an antidepressant in Denmark in 1989. Forest Laboratories markets the HBr salt of racemic citalopram formulated as a coated tablet (NDA 20-822, submitted May 7, 1997, approved July 17, 1998), and an oral solution (NDA 21-046, submitted November 2, 1998, approved December 22, 1999). The citalopram molecule contains one asymmetric carbon with the clinical activity residing in the S-(+) stereoisomer. S-citalopram oxalate (Lu 26-054-O) was

discovered and patented by H. Lundbeck who has licensed the drug to Forest Laboratories. The method of synthesis of S-citalopram oxalate is based on the synthesis of racemic citalopram HBr. The manufacture of racemic citalopram HBr is described in Lundbeck's Type II [redacted] The desired S-enantiomer is obtained using commercial scale chiral separation of a late stage intermediate. The manufacture of S-citalopram oxalate is described in Lundbeck's Type II DMF [redacted] The Escitalopram Oxalate drug substance is released for manufacturing Escitalopram Oxalate Tablets based on the COA from Lundbeck and confirmation of identity by Forest. Forest will perform at minimum full release tests using the Lundbeck procedures on at least one lot of Escitalopram Oxalate drug substance per year. The drug substance release specifications provide adequate control of the identity, quality and purity of the drug substance used to manufacture Escitalopram Oxalate tablets. Drug substance stability is performed by H. Lundbeck, and is described in H. Lundbeck's Type II [redacted] Lundbeck's Type II was reviewed (see DMF Chemistry Review 3) on July 10, 2001 by Lorenzo Rocca, Ph.D. (HFD-120) and found adequate to support NDA 21-323.

Escitalopram Oxalate tablets are manufactured by [redacted] The inactive excipients are USP/NF grade, and the non-compendial excipient [redacted] film coat is adequately described in [redacted] Type IV DMF [redacted] The normal in-process and physical parameters (e.g., compression parameters, tablet testing frequency, appearance, running tablet weight, hardness, thickness, etc) are monitored during the manufacturing process to assure the quality of the final product.

Clinical supply tablets were of fixed weight (for blinding) while the commercial tablets are dose proportional with a common master blend used to manufacture the different strengths. Minor formulation changes have occurred during drug product development. The major formulation change made during development was the introduction of film coating for the tablets. Manufacturing changes in the final phase of development include introduction of a dose proportional Escitalopram oxalate formulation for the manufacture of the different strengths, introduction of manufacturing changes necessary to scale-up batch size [redacted] depending on strength) and introduction of the Intermediate Bulk Container (IBC) system for mixing and compression. The IBC system for commercial manufacture of Escitalopram Oxalate Tablets was discussed and agreed upon at the pre-NDA meeting. Three tablet lots (one of each strength) using the IBC system are currently on stability. The differences between the clinical and commercial formulations are not deemed great enough from a chemistry standpoint to cause concern that compatibility studies are needed.

Escitalopram Oxalate tablet release and stability specifications adequately test for the identity, strength, quality and purity of the drug product. The specifications of the known degradation products and unidentified impurities are consistent with current ICH guidelines.

Based on the 18-month controlled room temperature (25±2°C/60±5%RH) and 6-month accelerated (40±2°C/75±5%RH) stability results submitted for Escitalopram Oxalate Tablets, packaged as intended for commercial distribution in 30 count, 100 count and 1000 count HDPE bottles and [redacted], a 24–month expiration period (shelf-life), is acceptable when stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

B. Description of How the Drug Product is Intended to be Used

The recommended dose of Escitalopram Oxalate Tablet is 10 mg once daily for all patients. Patients not responding to a 10 mg dose may benefit from a dose increase to 20 mg after a minimum of one week.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-323 is recommended for approval from the CMC standpoint. The approval recommendation is based on the following:

- Forest laboratory has responded adequately to all CMC deficiencies listed in the Agency Deficiency Letter dated August 31, 2001.
- The applicant has provided adequate information to assure the identity, strength, quality and purity of the drug product. All facilities involved in the manufacture and control of the drug substance and drug product were found to have acceptable cGMP

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

LRocca/Date
HPatel (TL-acting)/Date
PDavid (PM)/Date

C. CC Block

Orig. NDA 21-323
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/HPatel

Chemistry Assessment

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lorenzo Rocca
1/23/02 12:49:07 PM
CHEMIST

Hasmukh Patel
1/23/02 01:03:24 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 19

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SUPPORTING DOCUMENTS:

TYPE/ NUMBER	SUBJECT	HOLDER/ SPONSOR	STATUS	REVIEW DATE	LETTER DATE
	Lu 26-054-O (oxalate)	Forest Laboratories, Inc	CMC reviews up to date	Not Applicable	Not Applicable
			Adequate	7/10/01	Not Applicable
			Adequate: sufficient data provided by Applicant	Not Applicable	Not Applicable
			Adequate	Reviewed by L. Rocca (HFD-120) on 8/21/01	Not Applicable
			Adequate	Reviewed by D. Christodoulu (HFD-120) on 8/11/99	Not Applicable
			Adequate: sufficient data provided by Applicant	Not Applicable	Not Applicable
			Adequate	Reviewed by Sue-Ching Lin (HFD-550) on 8/6/98	Not Applicable
			Adequate	Reviewed by L. Rocca (HFD-120) on 8/21/01	Not Applicable
			Adequate	Reviewed by L. Rocca (HFD-120) on 8/31/01	Not Applicable

RELATED DOCUMENTS: N/A

1. [redacted] Amendment 20: Lu26-054 (S-Citalopram); Chemistry Information Amendment – Primary Stability Matrix (12/21/99)
2. [redacted] Amendment 43: Lu26-054 (S-Citalopram); Chemistry information Amendment – Specification Revision (3/8/00)

CONSULTS: N/A

OTHER REQUESTS:

Request	Status	Status of Request
Establishment Evaluation	5 sites found acceptable; 5 sites await decision as to their acceptability	Submitted on 4/17/01 CFN 1523957: Acceptable based on profile on 4/17/01. CFN 2419749: Acceptable based on profile on 4/17/01. CFN 2436283: Acceptable based on District Recommendation 4/23/01. CFN 1422692: Acceptable based on profile on 4/17/01. CFN 1316245: Acceptable based on profile on 4/17/01. CFN 9616660: Inspection Performed on 8/06/01 (Form 483 issued) CFN 9613224: Inspection Scheduled on 7/17/01 (9/18/01 Insp. Date) CFN 9613225: Inspection Scheduled on 7/17/01 (9/21/01 Insp. Date) CFN 9611872: Inspection Performed on 8/13/01 (Form 483 issued) CFN 9612725: Assigned inspection on 4/20/01
Methods Validation	Pending	Will be submitted after all the CMC deficiencies have been addressed.

RELATED REVIEWS:

Pharmacology and Toxicology; Primary Reviewer, Paul L. Roney, Ph.D. (HFD-120)	Pharmacology and Toxicology review pending as of August 31, 2001.
Clinical Pharmacology and Biopharmaceutics Review; Primary Reviewer, Iftekhar Mahmood, Ph.D. (HFD-860), completed 5/17/01. Team Leader, Raman Baweja, Ph.D. (HFD-860), concurrence, 5/17/01.	Not available in DFS as of August 31, 2001

REMARKS/COMMENTS: N/A

CONCLUSIONS & RECOMMENDATIONS: Concerning the chemistry, manufacturing, and controls (CMC), NDA 21-323 is approvable. The Applicant must address the deficiencies listed at the end of this review, before the NDA can be approved for CMC. An information request letter (August 31, 2001) has been sent to Forest Laboratories requesting that they address the deficiencies. Several sites involved in the manufacture of Escitalopram oxalate Tablets have yet to receive an Office of Compliance recommendation. An acceptable recommendation from the Office of Compliance will be required before this application can be approved for CMC. Based on the 12-month controlled room temperature (25±2°C/60±5%RH) and 6-month accelerated (40±2°C/75±5%RH) stability results submitted for Escitalopram oxalate Tablets packaged as intended for commercial distribution in 30 count, 100 count and 1000 count HDPE bottles and PVC/PVDC blisters a 24–month expiration period (shelf-life) is acceptable.

Lorenzo A. Rocca, Ph.D., Review Chemist

Robert H. Seevers, Ph.D., Chemistry Team Leader

cc:
Orig. NDA 21-323
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/RSeevers
File: C:\Data\Lr\Nda\Nda21323\N21323Review1.doc

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

27 pages

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/s/

Lorenzo Rocca
8/31/01 01:47:43 PM
CHEMIST

Robert H. Seevers
9/4/01 01:28:57 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL